Objections to claims

Claims 14, 16, 18, 23 and 25 have been objected to because the claims allegedly refer to non-elected diseases and additional active agents. Applicants respectfully traverse the objection on the grounds that it is clearly inconsistent with the Examiner's own restriction requirement in Paper No. 8.

However, in order to reduce issues and expedite prosecution, claims 13 and 17 have been amended to recite a method of treating diabetes rather than metabolic disease, and redundant claims 14, 18 and 25 have been canceled without prejudice.

With respect to claims 16 and 23, Applicants respectfully request that the Examiner clarify the restriction requirement, and treat Applicants previous designation of thiazolidinedione as a species election under 37 C.F.R.§ 1.146. Accordingly Applicants request that claims 16 and 23 be designated specific species claims, and accordingly request withdrawal of the objections to these claims.

Issues under 35 U.S.C. §112 first paragraph

Claims 13, 14, 16-18, and 25 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled such that a skilled artisan could use the invention commensurate in scope with the claims. Applicants respectfully traverse the rejection on the grounds that the currently pending claims are fully enabled by the present specification.

Firstly, Applicants have canceled claims 14, 18 and 25 and amended claims 13 and 17 to be consistent with the restriction requirement, such that all the currently pending claims are directed to methods of treating diabetes with an LXR agonist. As acknowledged by the Examiner on page 2, of the Action, the specification does provide an enabling disclosure for such a method.

Secondly, the present specification provides for specific disclosures enabling claims to methods of treating diabetes with an LXR agonist. For example, paragraph [0121] and Figure 15, disclose the use of a pan LXR agonist in a mouse model of diabetes, the (*db/db*) mouse, which displays diabetic symptoms such as obesity and severe hyperglycemia (elevated blood glucose). The data shows that administration of the pan LXR agonist to the diabetic mouse results in significant reduction in hyperglycemia (Figure 15), and Applicants

have therefore shown that the LXR agonist is an effective therapy for the treatment of diabetes.

For the above reasons, Applicants respectfully request withdrawal of this rejection to currently pending claims 13, 16 and 17. Applicants further submit that the rejection is not applicable to new claims 29 to 36.

Applicants also respectfully traverse the Examiner's contention that the specification allegedly necessitates undue experimentation. The Examiner presented an undue experimentation analysis based on the six factors presented in *In re Wands* (858 F.2d at 731,737, 8 U.S.P.Q. 2d at 1400, 1404 (Fed. Cir. 1988)).

As discussed above, the currently pending claims are fully enabled by the present specification, and do not require undue experimentation for the following reasons:

(1) The breadth of claims: The currently pending claims specifically define the particular metabolic disease (diabetes) and are directed to the use of defined LXR agonists.

(2) The absence or presence of working examples: Applicants provide a specific working example of an LXR agonist, and note that, working examples are not required to enable the breath of the pending claims and that "there is no magical relation between the number of representative examples and the breath of the claims". *In re Borowski and Van Venroy*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970).

(3) The state of the prior art and relative skill of those in the art: As pointed out by the Examiner, the prior art includes general LXR agonists such as those developed by Shan *et al.*

(4) The amount of direction or guidance presented and the quantity of experimentation necessary: Applicants point out that methods of administering drugs for the treatment or prevention of diseases are within the purview of a clinician of ordinary skill in the art, and therefore need not be provided, although general dosage information may be found in

paragraphs [0061]-[0075] of the specification.

(5) Predictability or unpredictability of the art: Applicants respectfully point to the experimental data showing the reduction of blood glucose in the diabetic mouse study upon treatment with an LXR agonist demonstrates the utility of the claimed method in a standard and well known model for the human disease. Such a result is novel and non-obvious over the prior art and represents an unexpected property applicable to LXR agonists. Additionally it is well settled that the disclosure of invention set forth by Applicants in their application must be given the presumption of correctness and operativeness by the PTO, and the only relevant concern of the PTO under the circumstances should be the truth of the assertions contained in the application. *In re Marzocchi*, 439 F.2d, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Examiner fails to proffer any evidence to controvert the truth of Applicants' assertions in the instant specification.

(6) Nature of the Invention: Applicants have shown that LXR agonists have specific utility for reducing hyperglycemia associated with diabetes.

Accordingly, it is Applicants' position that based on the teachings of the specification which the Examiner acknowledges enables practice of the claimed method with the disclosed species, the ordinary skilled artisan would be able to make and use the claimed methods without undue experimentation.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of pending claims 13, 16, 17 under 35 U.S.C. §112, first paragraph. Applicants further submit that the rejection is not applicable to new claims 29 to 36.

Issues under 35 U.S.C. §112 second paragraph

The Examiner has rejected claims 13, 14, 16-18, 21-23, 25 and 26 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection based on

the grounds that the currently pending claims both particularly point out, and distinctly claim the subject matter that Applicants' consider their invention.

Specifically the Examiner is of the opinion that claims 13, 14, 16-18, 21-23, 25 and 26 lack an essential step in the method of treatment. Applicants respectfully submit that contrary to the Examiners assertion, the outcome of treatment is not an essential step of the claimed methods, but rather, the result that follows from carrying out the method. Hence, the outcome of the method need not be described for the method to meet the requirements of 35 U.S.C. §112, second paragraph.

Rejections of claims 14, 18 and 25 under this title are moot since they have been canceled. Claim 26 is not currently under consideration.

In view of the foregoing, it is Applicant's position that the pending claims are clear and definite to one of ordinary skill in the art. Accordingly, Applicants respectfully requests reconsideration and withdrawal of this rejection of claims 13, 16, 17, and 21-23 under 35 U.S.C. §112, second paragraph.

Rejection of Claims Under 35 U.S.C. §102(b)

Claims 21 and 22 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Shan *et al.*, (WO 01/3705, Jan. 2001). Applicants respectfully disagree.

Shan *et al.* teaches the use of LXR agonists to raise the plasma level of high-density lipoprotein (HDL) in a human at risk of developing atherosclerosis, or having an atherosclerotic-associated disease (Claims 1, 22 and 23 of Shan *et al.*). By contrast, the current claims relate to methods of treating type II diabetes in a mammal by administering a therapeutically effective amount of an LXR agonist.

Although Shan *et al.* discloses that diabetics are at risk of developing atherosclerosis, Shan *et al.* does not disclose nor suggest the use of LXR agonists as a treatment for type II diabetes. Rather, Shan *et al.* is focused exclusively on methods to raise plasma HDL to treat or prevent atherosclerotic disease progression in a broad group of patients at risk of developing atherosclerosis.

Accordingly the methods taught and claimed in Shan *et al.* are different from those taught and currently claimed. Applicants thus respectfully request withdrawal of this rejection to claims 21 and 22.

Rejection of Claims Under 35 U.S.C. §103(a)

Claims 21 to 23 have been rejected under 35 U.S.C.§103(a) as allegedly being unpatentable over Shan *et al.* in light of Piper (US Publication No. US2002/0177602 A1).

As discussed above, Shan *et al.* neither discloses, nor suggests the use of an LXR agonist for treating type II diabetes. By contrast, Shan *et al.* teaches the use of LXR agonists to raise plasma HDL as a means of preventing or treating atherosclerosis and associated diseases such as coronary heart disease, cerebrovascular disease and peripheral vessel disease.

By comparison to these diseases, diabetes is characterized by elevated levels of plasma glucose, (see for example page 22, paragraph 77 of the present specification). In type II diabetes, the control of glucose homeostasis is an important approach to the treatment of the disease. The present Applicants were the first to establish that LXR agonists reduce hyperglycemia in a diabetic mouse model, and therefore to establish that they can be utilized to treat type II diabetes, see for example page 22, paragraph 76 of the present specification.

Although the development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases may be relatively common secondary characteristics of patients with type II diabetes, they are neither the direct primary cause, nor common symptom of the disease, which is characterized by elevated levels of plasma glucose.

By contrast the development of atherosclerosis and related cardiovascular diseases are primarily the result of hyperlipidemia, and specifically hypercholesterolemia characterized by elevated levels of LDL cholesterol, (see for example paragraph 5 of the present specification). Increased LDL cholesterol is believed to contribute to the build up of cholesterol in macrophages, which are a major component of atherosclerotic plaques characteristic of advanced cardiovascular disease.

Accordingly the use of LXR agonists to raise plasma HDL for the treatment of atherosclerosis related diseases does not suggest, nor render obvious the use of LXR agonists to treat type II diabetes. Rather, as pointed out by the Examiner in the previous restriction requirement, these are patentably distinct and non-obvious inventions.

To establish a prima facie case for obviousness all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Given that Shan et *al*. does not treat or suggest the element of treating type II diabetes in pending claims 21, 22 and 23, Applicants assert that the Office has not established a prima facie case of obviousness.

Applicants accordingly request withdrawal of this rejection of claims 21 to 23.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks presented herein, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

REQUEST FOR INTERVIEW

Applicants would appreciate the opportunity to discuss any remaining issues, by phone, after the Examiner has reviewed this Response. Therefore, Applicants' representatives will contact the Examiner to set up a convenient time.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant

Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 509132000100.

Dated: April 29, 2003

Respectfully submitted,

By Karen Babyak-Dow

Karen B. Dow
Patent Attorney
Registration No.: 29,684
For Andrew Cubitt
Patent Agent
Registration No. 45,452

MORRISON & FOERSTER LLP
3811 Valley Centre, Suite 500
San Diego, California 92130
(858) 720-5100

APPENDIX A

Marked up version of all claims currently under examination upon entry of the present amendment.

13. (Currently Amended) A method for treating **[a metabolic disease]** **diabetes** in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR**[β selective]** agonist.

14. (Canceled)

16. (Reiterated) The method of Claim 13 further comprising administering to said mammal an additional active agent selected from the group consisting of an antihyperlipidemic agent; a plasma HDL-raising agent; antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: a cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; a sulfonylurea; a biguanide, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoid; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogue; insulin; phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine; dexfenfluramine; phentiramine; a β_3 adrenoceptor agonist agent; sibutramine; a gastrointestinal lipase inhibitor; a leptin; neuropeptide Y; enterostatin; cholecytokinin; bombesin; amylin; a histamine H_3 receptor; a dopamine D_2 receptor; melanocyte stimulating hormone; corticotrophin releasing factor; galanin; and gamma amino butyric acid (GABA).

17. (Currently amended). A method of preventing the onset of, reducing the risk of developing, or the risk of recurrence **of**, **diabetes** **[metabolic disease]**, said method

comprising administering to said mammal a therapeutically-effective amount of an LXR [β selective compound] **agonist**.

18. (Canceled)

21. (Reiterated) A method for treating type II diabetes in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist.

22. (Reiterated) A method for treating type II diabetes in a mammal and reducing the cardiovascular complications of type II diabetes, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist.

23. (Reiterated) The method of claim 22 further comprising administering an additional active agent selected from the group consisting of a sulfonylureas; a biguanides, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoids; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogues; and insulin.

25. (Canceled)

29. (New) The method of claim 13, wherein said treatment decreases hyperglycemia.

30. (New) The method of claim 13, wherein said treatment decreases insulin resistance.

31. (New) The method of claim 17, wherein said treatment decreases plasma glucose levels.

32. (New) The method of claim 17, wherein said treatment decreases insulin resistance.

33. (New) The method of claim 21, wherein said treatment decreases hyperglycemia.

34. (New) The method of claim 21, wherein said treatment decreases insulin resistance.

35. (New) The method of claim 22, wherein said treatment decreases insulin resistance.

36. (New) The method of claim 22, wherein said treatment decreases hyperglycemia.